

PATENT
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attachment

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Richard P. Woychik *et al.*

Serial No.: 09/103,846

Group No.: 1632

Filed: 06/24/98

Examiner: Jill D. Martin

Entitled: **ALLELIC SERIES OF GENOMIC
MODIFICATIONS IN CELLS**

**SUPPLEMENTAL INFORMATION
DISCLOSURE STATEMENT**

Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Dated: _____

9/12/01

By: _____


CLIFF CANNON-CIN

Sir:

The citations listed below, copies attached, may be material to the examination of the above-identified application, and are therefore submitted in compliance with the duty of disclosure defined in 37 C.F.R. §§ 1.56 and 1.97. The Examiner is requested to make these citations of official record in this application.

Also enclosed is a check for the fee set forth in 37 CFR §1.17(p) in accordance with 37 CFR §1.97(c) for filing an Information Disclosure Statement after the mailing date of a first Office action on the merits.

- Cohen-Tannoudji *et al.* (1998) "I-SceI-Induced Gene Replacement at a Natural Locus in Embryonic Stem Cells," *Mol. Cell. Biol.* 18:1444-1448. This reference discloses a two-step method which enhances homologous


recombination at a targeted locus in the villin gene in mouse embryonic stem cells. The first step involves introducing an I-SceI restriction site into the villin locus using homologous recombination by a targeting vector. In the second step, the cells are co-transfected with a plasmid which expresses nuclease I-SceI (a rare cutter endonuclease which initiates double strand breaks in the genome), and with a replacement plasmid which contains a sequence of interest, such as a reporter gene. Expression of the nuclease I-SceI leads to cleavage of the villin gene at the I-SceI site. The ensuing double strand break is repaired by gene exchange with the replacement construct, thus introducing the gene of interest into the repair locus. Unlike the claimed invention, the method of Cohen-Tannoudji *et al.* does not include the step of treating cells with a chemical agent. Rather, Cohen-Tannoudji *et al.*'s method involves transfecting cells with plasmids. Further, Cohen-Tannoudji *et al.* does not disclose using fertilized egg cell or cells of 2-cell embryos, but rather discloses using mouse embryonic stem cells;

- Dobrovolsky *et al.* (1996) "Development of Novel Mouse tk⁺/– Embryonic stem cell line for use in mutagenicity studies," Environmental and Molecular Mutagenesis 28:483-489. Dobrovolsky *et al.* discloses treating mouse embryonic stem (ES) cells with the chemical mutagen *N*-ethyl-*N*-nitrosourea (ENU). Mutant selection for clones that are resistant to trifluorothymidine (TFT) was done by growing the ENU-treated cells in the presence of TFT. TFT-resistant ES cell clones were isolated and used to determine cloning efficiency under different conditions. Dobrovolsky *et al.*'s methods are distinguished from the claimed methods since Dobrovolsky *et al.* does not disclose using fertilized egg cells or cells of 2-cell embryos. Also, Dobrovolsky *et al.* does not disclose (a) treating mouse embryonic stem cells with a chemical agent under conditions such that at least one modification is produced in substantially every gene in the mouse embryonic stem cells, and (b) treating isolated mouse embryonic stem cells with *N*-ethyl-*N*-nitrosourea under conditions such that the frequency of mutation in any one gene in the treated mouse embryonic stem cells is from 1/600 to 1/9,000; and

- Sehlmeier *et al.* (1994) "Lower mutation frequencies are induced by ENU in undifferentiated embryonic cells than in differentiated cells of the mouse in vitro," Mutation Research 324:69-76. Sehlmeier *et al.* discloses mutagenizing the HPRT locus in the mouse embryonic carcinoma (EC) cells, which are the pluripotent stem cells of teratocarcinomas, of line P19 using the chemical carcinogen ENU. Mutants were selected by growth in 6-thioguanine (6-TG). The number of 6-TG-resistant colonies was calculated in relation to the number of viable cells. However, Sehlmeier *et al.* is distinguished from the instantly claimed invention since Sehlmeier *et al.* uses embryonic carcinoma cells rather than the recited fertilized egg cell, cells of 2-cell embryos, and mouse embryonic stem cells.

This Information Disclosure Statement under 37 C.F.R. §§ 1.56 and 1.97 is not to be construed as a representation that a search has been made, that additional information material to the examination of this application does not exist, or that any one or more of these citations constitutes prior art.

Dated: September 12, 2001


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